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The Dendritic Hypothesis for Alzheimer's Disease Pathophysiology

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Abstract

Converging evidence indicates that processes occurring in and around neuronal dendrites are central to the pathogenesis of Alzheimer's disease. These data support the concept of a "dendritic hypothesis" of AD, closely related to the existing synaptic hypothesis. Here we detail dendritic neuropathology in the disease and examine how A β , tau, and AD genetic risk factors affect dendritic structure and function. Finally, we consider potential mechanisms by which these key drivers could affect dendritic integrity and disease progression. These dendritic mechanisms serve as a framework for therapeutic target identification and for efforts to develop disease-modifying therapeutics for Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) affects about five million Americans, and prevalence is rising [4]. Current treatments provide only modest benefit against clinical worsening [76,87], so there is considerable interest in identifying new treatments for AD. Extensive investigation of AD neuropathology revealed to Heiko Braak and colleagues that "the outcome of the Alzheimer's disease-related pathological process in general is not primarily determined by massive neuronal loss but, rather, is the result of enormous numbers of surviving nerve cells with limited functionality" [24]. Much of this neuronal dysfunction arises at the synapse. The "synaptic hypothesis" of AD is based on pioneering work by Robert Terry [185] and was formulated in several excellent and influential reviews [171,184]. Intensive investigation of the synaptic mechanisms underlying AD over the last several years has revealed that many of the key changes in AD and AD models occur on the postsynaptic side of the synapse, in the dendrite. Furthermore, extrasynaptic signaling in dendrites also plays an important role in AD models [20,123]. As reviewed in other articles in this special issue, we have only recently learned how great a role dendrites play in neuronal signaling and how frequently they are involved in disease. Thus, it is opportune to consider a closely related cousin of the synaptic hypothesis of AD, namely the "dendritic hypothesis" of AD.

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Here we provide the results of a systematic review of the literature on the role of dendrites in AD. We searched PubMed for “dendrit* alzheimer*”, which returned 1178 results. We reviewed each of these abstracts, and the full text when available, and grouped the publications into categories that are reflected in the organization of the review. In order to narrow our review to the literature most relevant to disease, we focused on mechanisms with support from human tissue that have been investigated mechanistically in models of AD. Furthermore, we chose to cite excellent reviews for conciseness where possible.

We first summarize the dendritic neuropathological abnormalities seen in human subjects with AD. Next, we examine how A β , tau, and AD genetic risk factors affect dendritic structure and function. Finally, we consider potential mechanisms by which these key drivers could intersect to affect dendritic integrity and disease progression. This “dendritic hypothesis” serves as a framework for therapeutic target identification and for ongoing efforts to develop disease-modifying therapeutics for AD.

2. Dendritic Pathologies are Hallmarks of AD

Before delving into the causative mechanisms and key proteins involved in dendritic pathophysiology in AD, we begin with a brief review of the human neuropathology data. Dendritic abnormalities in AD are widespread and occur in the early stages of the disease. Generally, dendritic abnormalities in AD fall into the following categories: (1) dystrophic neurites, (2) reduction of dendritic complexity, and (3) loss of dendritic spines.

2.1 Dystrophic neurites

Dystrophic neurites were observed in some of the first descriptions of AD pathology [69,173] (Fig. 1A,D). Dystrophic neurites are misshapen neuritic processes that are immunoreactive with antibodies against abnormal tau, and can arise from either axons or dendrites [180]. Although they sometimes appear as bulbous dilations on silver stains, upon quantitative analysis dendritic dystrophic neurites have normal width but increased curvature compared to normal dendrites, which are fairly straight [110]. Dendritic dystrophic neurites are present both in and around amyloid plaques (plaque-associated neuritic dystrophy) and apart from plaques (neuropil threads or neuritic threads). Neuritic threads may originate from aberrant dendritic sprouting [98].

Two points are important to emphasize regarding dystrophic neurites. First, computational modeling predicts that these changes in dendritic morphology would significantly alter dendritic signal integration and spike timing [110,120]. Second, neuritic dystrophy around plaques is reversible with immunotherapy targeting amyloid- β (A β) in a mouse model of AD [26]. Indeed, many of the dendritic abnormalities that we will discuss appear to be reversible, an important consideration as therapeutic targets for AD are considered.

2.2 Reduced dendritic complexity

The second major dendritic abnormality seen in AD is reduced dendritic complexity (Fig. 1B,E; reviewed in [7]). Reduced dendritic complexity is prominent in dentate granule cells [55,71] and in pyramidal neurons in hippocampal area CA1 and subiculum [70,86]. Of note, there is no reduction of dendritic complexity in CA3 neurons [72]. Two factors probably

contribute to this selective vulnerability: afferent supply and propensity to form neurofibrillary tangles (NFTs) (Table 1; ref [7]). Anderton et al. [7] propose that reduced dendritic complexity in dentate granule cells is driven by loss of afferents caused by widespread loss of entorhinal cortex neurons in AD [22,79]. Dentate granule cells are relatively spared from cell death in AD [199], which explains the sparing of dendritic complexity of CA3 neurons, since dentate granule cells provide their primary afferent supply. However, CA3 pyramidal neurons are also resistant to neuronal death in AD, which would predict sparing of most afferents onto CA1 pyramidal neurons. Thus, another factor is necessary to explain the widespread reduction of dendritic complexity in area CA1, which Anderton et al. propose is due to the high propensity of CA1 neurons to form NFTs. Finally, loss of dendritic complexity in subicular pyramidal cells is likely a result of both the loss of afferents from CA1 and NFT propensity [7].

The association between NFT propensity and dendritic complexity is consistent with the hypothesis that somatodendritic accumulation of tau plays a key role in AD pathogenesis (see section 4). But do NFTs directly cause dendritic pathology or are they simply a marker of a more toxic process? A study comparing several measures of dendritic complexity in tangle-bearing vs. non-tangle neurons in the same AD patients showed that dendritic trees were >50% larger in tangle-bearing neurons than in non-tangle bearing neurons [77]. This is somewhat counter-intuitive unless the toxic species is soluble tau, not NFTs, and the NFTs sequester soluble tau and thus provide some degree of protection. *In vivo* imaging supports this idea, showing that NFTs form in neurons in response to toxic events and tangle-bearing neurons are long-lived relative to neurons that do not form tangles [50]. A similar observation was made in neurons expressing mutant huntingtin; neurons that form huntingtin inclusion bodies are actually protected and soluble huntingtin appears to be toxic [11]. A recent review summarized the evidence for and against toxicity of various forms of tau with the same conclusion: a soluble form of tau is likely the most toxic [47]. This has been corroborated by a recent report specifically implicating oligomeric forms of tau as toxic [19]. Therefore, therapeutic strategies should be focused on pathways involving soluble forms of tau.

2.3 Spine loss

A marked loss of dendritic spines is the final major dendritic abnormality in AD patients (Fig. 1C,F). Specifically, widespread spine loss is seen in pyramidal neurons in both the cortex and hippocampus [31,66,135,168] and in dentate granule cells in the hippocampus [55,64,77]. As dendritic spines are major sites of synaptic contact [81], the reduction of dendritic spines in AD likely contributes to synaptic dysfunction. Furthermore, the fact that areas of cortex and hippocampus are most affected is consistent with the idea that dendritic abnormalities reflect a wider network effect on these regions involved in memory formation and storage (review in detail in [9]). As with neuritic dystrophy, spine loss is also reversible in an animal model of AD [175].

3. A β and Aberrant Dendritic Signaling in AD

All three genes that cause dominantly inherited AD involve A β processing (reviewed in [94]). Furthermore, a protective variant in one of these genes, *APP*, can reduce the risk of

late-onset, sporadic AD [104]. These data strongly implicate a causative role for A β in Alzheimer's disease. In this section, we consider the key ways that A β exerts detrimental effects specifically through dendrites. Interestingly, one study using sparsely expressed APP in organotypic slices demonstrated A β release from dendrites, which acted on nearby dendrites to reduce synaptic transmission [198]. However, it is unclear what forms of A β were involved or how widespread this phenomenon is. Here, we will focus not on A β release *from* dendrites, but rather on A β 's effects *on* dendrites, including observations that (1) A β binds selectively to dendrites through a variety of putative receptors, and (2) excessive A β is detrimental to the normal functioning of dendritic ion channels.

3.1 Dendritic A β receptors

A β 's preferential binding sites on a neuron are at the synapse, and this binding is selectively postsynaptic [115,116,214] (Fig. 2). Many potential A β receptors have been proposed and have been reviewed elsewhere [118]. Here we consider the most recent evidence for many putative A β receptors or mediators of A β signaling including: α 7 nicotinic acetylcholine receptors, prion protein, EphB2, NMDA receptors, metabotropic glutamate receptors (mGluRs), insulin receptors, neuroligin, β adrenergic receptors, integrins, and p75 neurotrophin receptors. The strength of the data that different proteins serve as A β receptors is quite variable, and for many of these receptors, the species of A β that binds has not been determined. It will be important to address this shortcoming in future studies, as the pathogenicity of various forms of A β is of significant therapeutic relevance. For example, a recent study elegantly showed that A β dimers and trimers isolated from AD brain (but not monomers, A β *56 oligomers, or protofibrils) can induce activation of the Src family tyrosine kinase, Fyn, in primary neurons [117]. More studies with this kind of experimental detail will help to parse out the most important forms of A β to target therapeutically.

α 7 nicotinic acetylcholine receptors (α 7nAChRs) are probably the most well established receptor for A β , and A β binds to α 7nAChRs with high affinity [196]. Although α 7nAChRs are predominantly presynaptic, they are also expressed postsynaptically where they regulate synaptic plasticity [96]. For example, postsynaptic α 7nAChRs are expressed in 70% of cortical synapses [121]. In AD brain tissue, α 7nAChRs colocalize with neuritic plaques and A β reciprocally co-immunoprecipitates with α 7nAChRs [196]. Furthermore, other studies have provided evidence for a functional (not just physical) interaction of A β and α 7nAChRs. For example, through site-directed mutagenesis, Tyr-188 was found to be important for activation of α 7-nAChRs by A β [186]. Furthermore, in primary neurons, A β -induced endocytosis of NMDA receptors is dependent on postsynaptic α 7nAChRs, calcineurin and STEP [176]. Other A β -induced signaling events shown to be α 7nAChR-dependent include chronic down-regulation of mitogen-activated protein kinase (MAPK) signaling [61], glycogen synthase kinase 3 β (GSK3 β) activation, and tau phosphorylation [18]. Overall levels of α 7nAChRs are decreased in AD patients [106,200] which is thought to result mainly from the loss of presynaptic cholinergic neurons [49,201].

Prion protein (PrP), a membrane-anchored glycoprotein, is one of the more recent but most investigated additions to the list of putative receptors for A β . It is expressed at the postsynaptic density, closely interposed with other postsynaptic A β effectors [43,190]. PrP

and A β interact in culture [117,119], and A β co-immunoprecipitates with PrP from human AD tissue [117]. The A β binding site on PrP has been mapped to residues 95–110 using recombinant PrP with deletions and by using antibodies to PrP [119]. A β (predominantly dimers) binding to PrP causes Fyn activation and tau phosphorylation [117] and/or NR2B phosphorylation [190]. The extent to which prion protein is required for A β -induced synaptic and cognitive dysfunction is controversial. PrP ablation or blocking antibodies prevent A β oligomer-induced LTP deficits in hippocampal slices [16,73,119], behavioral dysfunction in APP/PSen E9 mice [78], and cell death in mice injected with A β [113]. However, in other studies these effects of blocking PrP were not replicated, including effects on LTP [29,107] and behavior [14,39]. Variability between models, specifically in the form of A β present at various time points in these models, could account for the differing results [118]. Therefore, while it is clear that PrP is in close relation to important mediators of A β -induced dysfunction, it is still not clear if (or at what time point) PrP itself is an essential receptor for A β -induced dysfunction in the human disease.

EphB2 is a postsynaptic receptor tyrosine kinase that, through ephrin, regulates NMDA receptor recruitment to the membrane, calcium influx, spine formation, and downstream transcription factors essential in LTP [88,183]. It colocalizes with postsynaptic α 7nAChRs [127]. A β binds the fibronectin repeat of recombinant EphB2 and co-immunoprecipitates with EphB2 in homogenates from primary neurons [38]. Mechanistically, A β induces EphB2 degradation in the proteasome. This degradation contributes to decreased NR1 levels, decreased NMDA receptor currents, and impaired LTP [38]. Furthermore, EphB2 is depleted in the hippocampus in AD brain [174] and a mouse model of AD [38]. Although this data shows strong support for EphB2 as an A β receptor, corroboration by another group and/or in another mouse model would help verify these results.

A β also co-localizes and immunoprecipitates with the NR1 and NR2B subunits of NMDA receptors [52,116]. Additionally, A β co-immunoprecipitation with NR1 is blocked by antibodies to NR1, which is consistent with direct binding of A β to NR1 [52]. Therefore, NMDA receptors are certainly candidates as receptors for A β . However, it is also possible that A β simply co-localizes rather than directly interacts with NMDA receptors, and antibodies to NR1 could simply be blocking interactions of A β with nearby direct binders by steric hindrance. Regardless of if A β binds directly to NMDA receptors, it clearly shows functional interaction (see section 6).

mGluRs are localized to the neck of dendritic spines and potentiate calcium influx from NMDA receptors. In primary neurons, A β can bind at the membrane of excitatory synapses and cause abnormal clustering of mGluR5 at the synapse due to decreased lateral diffusion [159]. This led to increased mGluR5 signaling, calcium dysregulation, synaptic disruption and loss of NMDA receptors. A β co-immunoprecipitated with mGluR5 from synaptosomes, implicating mGluR5 as a potential A β receptor. Furthermore, A β -induced loss of NMDA receptors was prevented by mGluR5 ablation [159]. It is unknown if this mGluR5 clustering occurs in human AD brains. This study suggests that mGluR5 may be an A β receptor, or at least functionally interacts with A β . Indeed, this study also implicates PrP and NMDA receptors as potential A β receptors [159]. A recent study has corroborated and clarified these results by showing that mGluR5 serves as a signaling mediator between A β /PrP

complexes and intracellular Fyn kinase signaling [189]. The implications of this link are more thoroughly discussed in section 6.

The insulin receptor and IGF signaling have a complex and interesting interaction with A β (reviewed in [54]). Insulin receptors were originally thought to be a direct A β receptor from pull-down studies [219] but are more likely a part of a larger A β receptor complex at the postsynaptic density [53]. Insulin receptors are important in learning and memory [218] and insulin signaling is pro-survival and associated with Akt activation [169]. Mechanistically, A β induces insulin receptor down-regulation in an NMDA receptor- and calcium-dependent manner [219]. In agreement with this mechanism, insulin receptors are decreased in AD brain [137]. Restoring insulin improves cognitive performance in AD patients [158], and administration of insulin is currently in a phase III clinical trial (ClinicalTrials.gov ID# NCT01767909). These studies may provide an explanation for why patients with type 2 diabetes, who lack proper insulin signaling, show increased risk for developing AD [48]. Given the high prevalence of diabetes and the fact that insulin signaling decreases with age, which is the greatest risk factor for AD [42], clarifying these interactions further will be important.

Neurologin-1 (NL-1) is a postsynaptic cell-adhesion molecule in excitatory synapses that may have a role in synapse stability (reviewed in [58]). A recent study showed that A β binds the extracellular domain of NL-1 and acts as a nucleation factor in vitro [59]. Also, A β coimmunoprecipitates with NL-1 [59]. These preliminary experiments suggest NL-1 may be a receptor for A β but its significance is uncertain.

β 2 adrenergic receptor (β 2AR) is another potential receptor for A β . β 2AR is a G protein-coupled receptor expressed at high levels in the frontal, parietal, and piriform cortices, midbrain, medial septal nuclei and olfactory tubercle [12], and co-immunoprecipitates with postsynaptic density protein 95 (PSD-95) and other postsynaptic proteins [194]. β 2AR is part of the central noradrenergic system which regulates attention and processing of the environment to select, store and retrieve information [167]. A β binds β 2AR at an allosteric site on the extracellular N terminus [194]. A β co-immunoprecipitates with β 2AR but not with β 2AR lacking its N-terminus [194]. A β causes acute activation of β 2AR, which induces cAMP activation, PKA phosphorylation of GluR1 subunit, and AMPAR hyperactivity [194]. In an AD mouse model, β 2AR is decreased in the prefrontal cortex and A β causes internalization of β 2AR, and thus reduces β 2AR and AMPAR activity [195].

Integrins are transmembrane proteins with structural and signaling roles. Multiple studies show that blocking integrin subunits in vitro prevents the negative effect of A β . Antibodies to the α 2 β 1 and α 5 β 1 subunits prevent A β deposition and toxicity [204]. Furthermore, antibodies to the α 5 integrin subunit block A β -induced LTP deficits both in hippocampal slices and in vivo [197]. While integrins are present on both sides of the synapse, several observations suggest that A β -integrin interactions activate postsynaptic pathways, including Pyk2/paxillin [204] focal adhesion kinase (FAK) [85], and MAPK signaling [6]. These data suggests A β could be binding integrins directly or that integrins are in the proximity of A β receptors.

p75 neurotrophin receptors (p75^{NTR}) are transmembrane glycoproteins and nerve growth factor (NGF) receptors that modulate dendritic morphology and synaptic plasticity [212]. p75^{NTR} is a pan-neurotrophin receptor, in contrast to Trk receptor tyrosine kinases, which are ligand-specific [56]. Co-activation of p75^{NTR} with Trk receptors tends to have effects opposite of p75^{NTR} activation alone. A β co-immunoprecipitates with p75^{NTR} in cell culture [208]. p75^{NTR} is highly expressed on cholinergic basal forebrain neurons and A β -induced degeneration of cholinergic neurons is mediated by p75^{NTR} both in vitro and in vivo [177]. A β toxicity involves p75^{NTR} intracellular death domain activation [57] and phosphorylation of JNK leading to cell death [46]. p75^{NTR} levels are increased in the hippocampus in AD brains [33].

3.2 A β affects dendritic ion channels

Higher than normal levels of A β cause excitation–inhibition imbalance (reviewed in [150]). Dysfunction of dendritic ion channels may contribute to this dysfunction. Here we consider A β 's effects on calcium, sodium, and potassium channels that are expressed in dendrites and regulate neuronal excitability. Modulation of these ion channels may provide potential avenues for new AD therapeutics.

A β -induced calcium dysregulation is a critical component of dysfunction in AD. We have already discussed the possibility that A β may bind to calcium-permeable NMDA receptors and we will further discuss A β -induced NMDA receptor signaling abnormalities in section 6. Here, we consider A β 's effects on voltage-gated calcium channels (VGCCs). Ca_v1.2 channels are L-type VGCCs that are located both extrasynaptically and in dendritic spines [146]. In the hippocampus, Ca_v1.2 channels normally regulate signaling to the nucleus and synaptic plasticity [62,139], but excessive activation can result in excitotoxicity and neurodegeneration [179]. In neuronal cultures, A β induces MAPK phosphorylation of Ca_v1 channels [65] and increased calcium influx through Ca_v1 channels, causing neurotoxicity [90,188]. In an AD mouse model, Ca_v1.2 is enriched in dendrites and in reactive astrocytes associated with plaques [202]. AD brain tissue shows increased Ca_v1 expression in the hippocampus [45].

As a potential major source of A β -induced calcium entry, VGCCs provide a potential therapeutic target. Early clinical trials with calcium channel blockers including MEM-1003 and nimodipine did not provide clear evidence of benefit [74,128]. However, next-generation compounds optimized for dementia treatment that are more selective and state-dependent may have promise and await testing in animal models [145]. Two compounds in particular, TROX-1 [1] and A-1048400 [170], show potent inhibition of pre-synaptic VGCC activity, are blood brain barrier-permeable, and show state-dependence. These or similar compounds designed to target L-type channels, such as a recently developed Ca_v1.3 specific antagonist (which avoids unwanted cardiac effects of Ca_v1.2 inhibition) [105] in animal models, may provide a more definitive test of the hypothesis that targeting VGCCs has promise in AD.

Other channels that regulate neuronal excitability show disruption from excessive A β , such as the voltage-gated sodium channel Na_v1.1. Na_v1.1 is decreased in the parietal cortex of AD brains, and shows highest expression in cell bodies and dendrites where it is thought to

regulate integration of signals traveling from the dendrites to the soma [187]. $\text{Na}_v1.1$ is expressed in both excitatory and inhibitory neurons [187]. In an AD mouse model, $\text{Na}_v1.1$ is decreased in the parietal cortex, specifically in parvalbumin positive GABAergic interneurons [191]. This decrease in $\text{Na}_v1.1$ contributes to the depressed GABA oscillations and increased network hypersynchrony seen in these mice [191].

Another potential $\text{A}\beta$ -sensitive modulator of neuronal excitability is the A-type voltage-gated potassium channel $\text{K}_v4.2$ [17]. The potential role of $\text{K}_v4.2$ in regulating dendritic excitability in AD has been reviewed elsewhere [143]. $\text{K}_v4.2$ has highest expression in distal dendrites of the hippocampus and cerebellum where it regulates back-propagating action potentials and dendritic excitability [35,91]. $\text{A}\beta$ blocks A-type currents in multiple neuronal culture models [102,210,216]. Furthermore, hippocampal slices treated with $\text{A}\beta$ showed decreased A-type currents, increased back-propagating action potentials, increased dendritic membrane excitability, and increased calcium levels in CA1 pyramidal neurons [34]. An intriguing open question is if A-type currents are altered in mouse models of AD as well.

4. Dendritic mislocalization of tau is a key event in AD

Tau protein is the major component of NFTs in AD [111,203]. It plays a critical role downstream of $\text{A}\beta$, with multiple studies showing that tau reduction (e.g., in tau knockout mice) has strong beneficial effects in AD models, including models overexpressing Fyn kinase [8,93,99,161,162,172,192]. Tau reduction seems to exert beneficial effects by reducing the susceptibility of neurons to hyperexcitability, which is likely an important driver of excitation-inhibition imbalance in AD (reviewed in [150,151]). In this way, tau reduction (or strategies aimed at recapitulating the benefits of tau reduction) could counteract the dendritic signaling abnormalities induced by $\text{A}\beta$.

Tau exhibits several abnormal characteristics in AD including aggregation, abnormal posttranslational modifications, somatodendritic mislocalization (Fig. 3), and (most recently) a putative role as a cell-to-cell transmissible protein. Tau aggregation and hyperphosphorylation have been extensively studied in AD and were recently reviewed elsewhere [134,140,178]. Cell-to-cell transmission of tau is a new area of research under intensive investigation by numerous labs [23,51,92,125,153,154]. Although there are clearly potential consequences for dendritic health from cell-to-cell transmission of tau, we will focus here on dendritic mislocalization of tau. Under normal conditions, tau is primarily an axonal protein (Fig. 3A). Tau is also present in dendrites, but at much lower levels; tau co-immunoprecipitates with PSD-95 [32,99,138], but generally is not visible in dendrites by light microscopy. In AD, tau is mislocalized into dendrites, becoming easily visible by immunostaining (Fig. 3B). Furthermore, dendritic tau mislocalization can be induced by exogenous application of $\text{A}\beta$ onto primary neurons (Fig. 3C,D) [215]. Dendritic tau mislocalization is an early event in AD pathogenesis, probably occurring in the preclinical stages of the disease and before tau aggregation [21,25]. In this section, we consider recent mechanistic work aimed at determining (1) factors that control dendritic mislocalization of tau and (2) the role of dendritic tau in AD.

4.1 Determinants of dendritic mislocalization of tau

A β can induce tau mislocalization into dendrites. Treating cultured neurons with A β oligomers induces dendritic tau mislocalization [214,215]. Transgenic mice expressing A β also have increased levels of somatodendritic tau, which can be reduced by inhibiting A β production through genetic reduction of BACE, the beta-secretase that initiates A β cleavage from APP [32]. However, it is not clear that A β is the primary driver of tau mislocalization in AD, because dendritic tau is an early event observed in regions that do not have significant increases in A β levels [25]. Therefore, it is possible that tau mislocalization either provides a backdrop on which A β can act or is already in progress and accelerated by increased A β levels. Alternatively, perhaps some combination of these two possibilities is at play. In any case, tau mislocalization certainly appears to be permissive for the detrimental effects of A β , as we will discuss.

Phosphorylation of tau correlates well with dendritic mislocalization, especially phosphorylation in the microtubule-binding domains. Unmodified tau has a high affinity for microtubules [44]. However, phosphorylation of tau at KXGS motifs in each microtubule-binding domain dramatically reduces microtubule binding [124]. These KXGS sites are modified specifically in AD and not in other tauopathies, which suggests that this modification of tau may be uniquely important for the progression of AD [155]. KXGS sites are phosphorylated by microtubule affinity-regulating kinase (MARK, also known as PAR-1), or by adenosine monophosphate-activated protein kinase (AMPK) [133]. Activation of MARK/PAR-1 or AMPK, leading to subsequent phosphorylation of KXGS sites in tau, is critical for the synaptotoxicity and dendritic spine abnormalities induced by A β [83,133,211].

Phosphorylation in the proline-rich domain of tau, particularly at the AT8 sites, may also contribute to, or at least correlates with, dendritic mislocalization. AT8, which recognizes tau phosphorylated at serine 202 and 205, labels tau mislocalized to dendrites in AD (Fig. 3B) [103,215]. These sites are also phosphorylated early in disease, before significant neuritic abnormality is observed [21,25]. Taken together, there is strong evidence that dendritic tau is phosphorylated at both the KXGS sites and the AT8 site. Indeed, two recent studies described tau phosphorylation at KXGS sites and the AT8 epitope (with activation of the associated kinases, MARK and CDK5) in dendrites; in contrast, other phosphoepitopes such as PHF-1 and AT180 were not phosphorylated and there was no activation of GSK-3 β [103,215]. This suggests that tau can be partially, but not completely, phosphorylated in dendrites, at least during certain stages of disease. These studies also offer some explanation for why somatodendritic localization of tau can be seen independent of NFT pathology in AD [112], and for why tau phosphorylation is progressive at different phosphoepitopes from pre-tangle through tangle stages [13].

Tau acetylation can also impair tau's interaction with microtubules [41], and tau pseudophosphorylation at KXGS sites can potentiate tau auto-acetylation activity (the only implicated enzymatic activity of tau), providing a potential pathogenic positive feedback loop for a somatodendritically mislocalized form of tau [40]. Though the full consequences of tau dissociation from microtubules remain to be determined, it is clear that in disease, tau dissociates from microtubules and mislocalizes to the somatodendritic compartment.

Although these post-translational modifications correlate with somatodendritically mislocalized tau, a recent study has called into question whether these modifications are truly causative in triggering mislocalization of tau. In primary neurons treated with A β , newly synthesized tau is missorted to the somatodendritic compartment by an unknown mechanism, then later phosphorylated by MARK in the dendrites [213]. Further work will be needed to determine if phosphorylation at these key residues is causative for the somatodendritic mislocalization of tau *in vivo*.

4.2 A soluble form of tau mediates dendritic abnormalities

The observation that A β can cause aberrant mislocalization and at least partial phosphorylation of tau in the dendrites suggests that there may be a role for soluble, pre-tangle tau in the dendrites (see preceding discussion in section 2.3). What are the consequences of this unwelcome presence of soluble tau in the dendrites? Two distinct gain-of-function roles of soluble, pre-tangle tau have been proposed.

One report suggested a gain-of-function role for soluble dendritic tau involving increased targeting of Fyn to the synapse [99], where it can phosphorylate the NR2B subunit of the NMDA receptor [142,164], potentially leading to excitotoxicity. Dendritic tau is also in complex with PSD-95, adding more evidence to the idea that tau could be assuming a role as an aberrant synaptic scaffolding protein [32,99,138]. Furthermore, tau localizes to spines and mediates synaptic dysfunction preceding neuronal loss, again suggesting a key role for tau in the dendrites [95].

Another gain-of-function role of soluble dendritic tau was proposed by a recent provocative study suggesting that the presence of tau, not the absence, actually leads to microtubule destabilization [213]. A β is associated with tau-dependent accumulation of tubulin tyrosine ligase-like 6 (TTL6) into dendrites, which catalyzes polyglutamylation of microtubules. Polyglutamylated microtubules recruit spastin, which cleaves microtubules.

A β toxicity could be reduced by RNAi against spastin. This proposition that a gain-of-function, rather than loss-of-function, role of tau contributes to microtubule destabilization serves as an important bridge between two seemingly contradictory observations: that both tau reduction (presumably blocking a gain-of-function role of tau) and microtubule stabilizers (presumably blocking a loss-of-function of tau, reviewed elsewhere [15]) are protective in AD models. The concept of tau-dependent, spastin-mediated microtubule destabilization [213] provides a framework for understanding how both tau reduction and microtubule stabilization might be viable and perhaps even interconnected therapeutic options.

5. Genetic risk factors for AD confer susceptibility to reduced dendritic health

The E4 isoform of apolipoprotein E (apoE4) is, by far, the strongest genetic risk factor for late-onset AD and is highly enriched in the AD patient population [68]. Furthermore, apoE4 causes reduced spine density, synaptic integrity, and dendritic complexity in mouse models [10,63,100,109,163]. ApoE has been implicated in a multitude of processes that could

contribute to AD, and the various ways that apoE4 confers higher AD risk remains an area of active investigation (reviewed in [131]). However, two roles of apoE are clearly directly related to dendritic health: (1) apoE4 results in reduced A β clearance, and (2) apoE is produced in neurons in response to injury, with effects on dendritic integrity.

The first direct relation to dendritic health is a role for apoE4 in reduced A β clearance, in both AD and models of AD [30]. Additionally, other lower-impact genetic risk factors for late-onset AD, including *CD33* and *ABCA7*, also affect A β clearance [82,108]. The fact that late-onset AD genetic risk factors affect A β clearance is not surprising, and is in agreement with the strong causative effect of A β processing mutations in autosomal dominant AD. We have already established the detrimental effects of A β on dendritic health (see section 3), so apoE4 and other genetic AD risk factors affecting A β clearance are likely to have detrimental effects on dendritic health through the A β -dependent pathways discussed above.

The second direct relation to dendritic health is that apoE is produced in neurons in response to injury. ApoE is primarily expressed in astrocytes [130]. However, in response to injury, neurons can produce apoE as a mechanism for membrane repair (reviewed in [132]). However, instead of providing repair and protection, neuronal apoE4 has detrimental effects on neurons [28,100]. Importantly, neuronal apoE4 is specifically responsible for detrimental effects on dendrites including loss of dendritic spines and arborization [100]. These studies raise the question of what molecular mechanism may drive the toxicity of apoE4. Two factors are likely important: (1) apoE4 uniquely undergoes an aberrant interaction between its N- and C-terminal domains and (2) apoE4 is uniquely susceptible to the generation of toxic fragments [97,132]. One therapeutic approach in development is the use small molecule “structure correctors” to disrupt the aberrant N to C-terminal interaction, making apoE4 more like the other apoE isoforms [27].

6. Unifying mechanisms underlying dendritic abnormalities in AD

We have discussed a number of discrete interactions by which A β and tau can cause dendritic abnormalities in AD. How can we combine these observations about dendritic abnormalities in AD into a unified model? Here we consider key signaling cascades downstream of A β that could induce the dendritic signaling and morphological abnormalities we have discussed. Because so many pathways have been implicated in various model systems, here we have emphasized those with supporting evidence from studies in human tissue.

There is considerable evidence in human tissue, as well as in model systems, that processes occurring around the NMDA receptor supercomplex in the postsynaptic density are critical for mediating dendritic abnormalities in AD (Fig. 4). A β initiates these events, and may work through one or many of the receptors discussed in section 3.1. Regardless of how A β initiates abnormalities, it is clear that in AD, the levels of several critical neurotransmitter receptors are reduced, including AMPA receptors, NMDA receptors, and α 7nACh receptors [84,152,182,193]. Table 2 includes these and other key proteins with altered levels, function, or localization in AD brain tissue, many of which are involved in our proposed model (Fig. 4). Evidence from model systems is consistent with an initial potentiation of synaptic

transmission by A β [2,75,156]. This potentiation causes an increase in calcium influx through NMDA receptors and α 7nACh receptors [126,176], which can then activate several signaling cascades, including calcineurin/calpain and Fyn kinase, which work in concert to cause excitation-inhibition imbalance and dendritic abnormalities.

6.1 Activation of Ca²⁺ cascades

Activation of calcineurin and downstream activation of the transcriptional factor nuclear factor of activated T-cells (NFAT) is a well-studied mediator of dendritic abnormalities in AD models. Through this pathway, A β can induce the three hallmarks of dendritic dysfunction we discussed in section 2 (dystrophic neurites, reduced dendritic complexity, and spine loss) [205]. Furthermore, nuclear translocation of calcineurin and NFAT in AD has been observed [205,206]. These detrimental effects are ameliorated by either calcineurin inhibition or specific inhibition of the calcineurin-NFAT interaction in model systems [60,157,165,205,206].

Calcineurin (CaN) can also activate striatal-enriched phosphatase (STEP), which too is increased in AD [114]. CaN-induced STEP activation causes NMDA receptor endocytosis at the synapse [176]. Concurrent with CaN activation, calcium can activate calpain to cleave extrasynaptic STEP to an inactive form, leading to the combined phenotype of enhanced extrasynaptic NMDA receptor signaling and attenuated synaptic NMDA receptor signaling [122,123,207]. STEP reduction protects against behavioral abnormalities in a mouse model of AD, indicating the importance of this pathway [217]. Furthermore, extrasynaptic NMDA receptor activation has been implicated in calpain-mediated tau toxicity [5], double-stranded DNA breaks [181], and increased A β production [20] in models of AD, indicating the centrality of this pathway. Other downstream consequences of increased intracellular calcium levels could include widespread s-nitrosylation of proteins by nNOS, which is coupled to the NMDA receptor through PSD-95 (reviewed exhaustively elsewhere [141]).

6.2 Activation of Fyn kinase

In addition to activation of calcineurin, A β can also activate the Src family kinase Fyn in AD [117]. The importance of Fyn activation in AD has received support by recent genetic evidence from an unbiased screen that variants in Fyn can affect AD age-of-onset in ApoE4 carriers [160]. Here we consider (1) the potential mechanism for Fyn activation, (2) downstream substrates of Fyn, and (3) downstream consequences of Fyn signaling.

When considering Fyn's activation, it is interesting to note that Fyn activation persists in AD despite the fact that it is a substrate for STEP, a phosphatase that normally dephosphorylates and inactivates Fyn and is increased in AD [144]. One reason that Fyn activation persists despite increased STEP may be that Fyn is activated downstream of PrP, which is also upregulated in AD [117,190]. Thus, activation of Fyn by PrP could outcompete downregulation of Fyn by STEP. Detailed studies have shown that an A β /PrP complex works through mGluR5 to activate Fyn kinase [189], and that activation of Fyn by PrP is specifically mediated by dimer or trimer forms of A β [117].

Fyn has two well characterized downstream substrates in AD and AD models: tau [117] and the NR2B subunit of the NMDA receptor [99,190]. Most studies have focused on NR2B.

Work in model systems suggests that Fyn temporarily sustains enhanced signaling through the NMDA receptor by phosphorylating the NR2B subunit of the NMDA receptor on Y1472 (pNR2B). Specifically, in primary neurons treated with A β , Fyn is activated and NR2B phosphorylation at Y1472 is increased with a corresponding increase in its surface expression and of intracellular calcium levels [176,190]. Subsequently, this signaling is attenuated by increased STEP levels, leading to decreased pNR2B and intracellular calcium levels below baseline [190]. This observation is consistent with the observation that in 4-month-old APP23 mice, pNR2B levels are significantly increased in a hippocampal fraction of PSD-associated proteins [99]. Also in agreement with this model, at time points later than 4 months, pNR2B levels are decreased in the hippocampus in Tg2576 mice, J20 mice, and in human tissue [114,147,148,182].

What are the consequences of increased Fyn signaling in AD? One consequence is likely tau-mediated deficits, and we have discussed the emerging role for dendritic tau in facilitating this pathway in concert with Fyn (section 4.2). Consistent with this notion, deficits in an AD model that depends on Fyn kinase overexpression are tau-dependent [161]. Other downstream consequences of Fyn activation may include feedback to further increase α 7nAChR expression, a potential positive feedback loop potentiating dysfunction in AD [36]. Furthermore, Fyn may lead to spine loss by activating a PAK/LIMK1/cofilin cascade through Tiam1 (reviewed elsewhere [129]).

Taken together, many studies suggest that Fyn is another critical mediator of dendritic abnormalities in AD. Because loss of normal Fyn function is detrimental to learning and memory [80,136], it will likely be necessary to find a disease-specific alternative to traditional kinase inhibitors in order to therapeutically address the role of Fyn in AD. One example of an alternative could include targeting upstream signaling to prevent Fyn activation, such as mGluR5 negative allosteric modulators, which ameliorate behavior deficits in AD models [189]. Another alternative to traditional kinase inhibitors is blocking Fyn trafficking to the dendrites, since decreasing the amount of dendritic Fyn correlates with improvements in an AD mouse model [99]. However, it is possible that partial inhibition of Fyn kinase activity could still provide benefit, and the process of testing this hypothesis has begun with a phase I clinical trial of a Fyn kinase inhibitor in AD (ClinicalTrials.gov ID# NCT01864655).

7. Conclusions and Future Directions

We have discussed the importance of dendrites in AD by describing the extensive dendritic neuropathological changes, the key factors leading to those changes, and potential unifying mechanisms. Dendrites are key sites of signal processing for normal brain function, so it is clear that the disruption of dendritic integrity in key memory circuits would contribute to AD. A few important ideas should be considered when approaching therapeutic development targeting dendritic integrity. First, A β has an endogenous role in synaptic plasticity. Therapeutics aimed at A β and at cascades downstream of A β will therefore need to be carefully developed so that normal synaptic function is left intact. Careful biochemical analysis of the pathogenic species of A β in a given system will therefore be an important step to standardize in future studies. Second, tau is for the most part an uninvited guest in the

dendrites. As such, signaling cascades involving tau are likely to be attractive therapeutic targets for addressing dendritic abnormalities in AD, as reducing disease-specific dendritic roles of tau is unlikely to affect normal dendritic function. Finally, genetic risk factors for AD, particularly apoE4, are important modifiers of dendritic health. Therefore, it is not surprising the apoE genotype has proven to be an important variable affecting responses in several recent clinical trials and future trials are likely to be increasingly stratified by apoE genotype.

One can imagine numerous therapeutic targets based on the mechanisms discussed here, and we have proposed several specific ones. However, the fact that these mechanisms have been the most studied and shown the most promise to date does not preclude the existence other important possibilities. We expect that increased understanding of the interplay of A β , tau, and genetic risk factors will unmask new therapeutic avenues to explore in the coming years.

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Highlights

Dendritic neuropathology is ubiquitous in Alzheimer's Disease (AD).

A β causes dendritic neuropathology in AD.

Dendritic mislocalization of Tau is an early feature of AD.

Tau mediates dendritic dysfunction in AD models.

Addressing dysfunctional dendritic pathways holds promise for AD treatment.

Figure 1.

Types of dendritic pathology in AD. (A,D) Neuritic dystrophy in AD, compared with control. The molecular layer of the subiculum was stained for MAP2. Images reproduced from [67] with permission. (B,E) Reduced dendritic complexity in AD, compared with control, in Golgi-stained hippocampal CA1 pyramidal cells. Images reproduced from [209] with permission. (C,F) Reduced spine density in a 56-year-old AD patient, compared with a 58-year-old control, in layer III pyramidal neurons. Images reproduced from [31] with permission.

Figure 2.

A β oligomers bind selectively to dendrites. Cultured hippocampal pyramidal neurons were treated with A β oligomers, then immunostained. (A,B), A β -treated neurons were double labeled for A β (green) and postsynaptic density protein 95 (PSD-95, red), showing colocalization (yellow). (C) Double labeling for A β (green) and the presynaptic marker synaptophysin (red) shows juxtaposition, but not colocalization. (D,E). Double labeling for A β (green) and the postsynaptic protein α CaMKII (red) shows binding to dendritic spines. Images reproduced from [115] with permission.

Figure 3.

Tau mislocalizes to the dendrites in AD. (A) Tau (red) is normally localized to the axon. A primary hippocampal neuron was stained with MAP2 to label the dendrites (blue), β IV spectrin to label the axon initial segment (green), and tau (red). Image reproduced from [101] with permission. (B) In AD, tau mislocalizes to the dendrites. Pyramidal neurons in the deep transentorhinal cortex from a patient with AD were stained with AT8. Image reproduced from [21] with permission. (C,D) Under control conditions, tau is excluded from the dendrites as indicated by the absence of colocalization with MAP2, but with the addition of A β oligomers (A β -derived diffusible ligands, ADDLs), tau mislocalizes to the dendrites (white arrows show a MAP2-positive dendrite with tau immunoreactivity). Images reproduced from [215] with permission.

Figure 4.

Key mechanisms of dendritic abnormality in AD. Aβ can cause a transient rise in calcium through α7nACh and NMDA receptors, leading to a transient synaptic potentiation, followed by synaptic depression mediated by STEP activation and EphB2 depletion [38,176,190]. Loss of receptors at the synapse is indicated by light shading. Extrasynaptically, Calpain can cleave STEP, allowing activated Fyn to keep NR2B-containing NMDA receptors at the surface, leading to extrasynaptic potentiation [123,207]. These events can also lead to toxic CaN/NFAT signaling and phosphorylation of tau [117,205].

Table 1

Factors affecting susceptibility of regions in the hippocampal circuit to reduced dendritic complexity. See ref. [7] for details.

	Entorhinal Cortex	Dentate Gyrus	CA3	CA1	Subiculum
Cell Death	✓			✓	
Afferent Loss		✓			✓
NFT Propensity	✓			✓	✓
↓ Dendritic Complexity		✓		✓	✓

Key proteins with altered levels or function in AD brain tissue. Note that several of the proteins listed here are included in our unifying model (Fig. 4).

Table 2

Protein	MCI	AD	Region	Cognition	Correlation	Ref.
NR1, NR2B	→	↓	EC & Hippocampus	✓		[182]
P-NR2B	→	↓	Entorhinal cortex	✓		[182]
α7nAChR		↓	Hippocampus			[84]
mGluR	→	↓ binding	Cortex	✓		[3]
AMPA		↓	Entorhinal cortex			[193]
EphB2		↓	Hippocampus			[174]
Calbindin		↓	Dentate gyrus	✓		[149]
PrP ^{sc}	→	↑	Inferior temporal gyrus			[117]
Dendritic Tau	↑	↑	Entorhinal cortex			[21]
Fyn	→	↑ insoluble	Frontal cortex	✓		[89]
P-Fyn	→	↑	Inferior temporal gyrus			[117]
STEP		↑	Cortex			[114]
CaN/NFAT		↑ nuclear	Cortex			[205]
Calpain		↑	Frontal cortex			[166]
SNO-Drp1		↑	Frontal cortex			[37]

→ indicates no change; checkmarks under cognition correlation indicate changes that had a significant correlation with cognitive outcome measures.